MS.ID-IJPBS-7313
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2022) 12 (2): 38-44
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Novel Drug Delivery Approach to Enhance Absolute Bioavailability of Ciprofloxacin by Topical Application

Varsha Gajanan Rane*[1], Sanket Mukund Gandhi[1], Vijay Arjun Jagtap[1], Megha Sanjay Jadhav[1] and Shubham Vijay Desai[1]

[1]Department of Pharmaceutics, Yashwantrao Bhonsale College of Pharmacy Sawantwadi, Maharashtra, India.

Received: 12 Jan 2022 / Accepted: 6 March 2022/ Published online: 01 April 2022
***Corresponding Author Email:** ceuticsybcp@gmail.com

Abstract

The purpose of writing this review is to study the effect various novel drug delivery approach such as ethosomes, liposomes, niosomes, micells, nanoparticles, aspasomes, microsponges, microemulsions, hydrogels and solid lipid nanoparticles etc on absolute bioavailability of ciprofloxacin at site of action. The current review emphasizes the potential of various novel drug delivery strategies in optimizing and enhancing the topical delivery of ciprofloxacin.

Keywords

Nanoparticles, Ciprofloxacin, Bioavailability, TDDS, NDDS.

*****

INTRODUCTION

Ciprofloxacin is a second-generation fluoroquinolone antibiotic that is used to treat bacterial infections such as urinary tract infections and pneumonia. The FDA has approved ciprofloxacin for the treatment of urinary tract infections, sexually transmitted infections (gonorrhoea and chancroid), skin, bone, and joint infections, prostatitis, typhoid fever, gastrointestinal infections, and lower respiratory tract infections, anthrax, plague, and salmonellosis. Furthermore, ciprofloxacin is an appropriate treatment option in patients with mixed infections or those who are predisposed to Gram-negative infections. Ciprofloxacin was patented in 1983 by Bayer A.G. and approved in 1987 by the United States Food and Drug Administration (USFDA).[1]

Solubility and bioavailability data indicate that ciprofloxacin hydrochloride is a BCS Class IV drug (low solubility/low permeability). Ciprofloxacin has low water-solubility, Because of the low water solubility, ciprofloxacin is formulated into tablets for oral use as monohydrochloride monohydrate salt. In this form, its absolute bioavailability is of 60%. Alternatively, a ciprofloxacin base has been formulated in oil-based syrups with a better bioavailability of up to 70%. Formulations for topical use (e.g., ciprofloxacin ophthalmic ointment) are made by dissolving the drug in mineral oil. Ciprofloxacin antibiotics are not used for the topical treatment of skin disease due to insufficient drug bioavailability and the possibility of local side effects due to their low permeability. As a result, novel drug delivery approaches such as ethosomes and liposomes can help to improve ciprofloxacin bioavailability. Recent advancements in the understanding of drug pharmacokinetic and pharmacodynamic behaviour have provided a more rational approach to drug distribution. Novel drug delivery systems (NDDS) are carriers that keep drug concentrations in the therapeutic range for a longer duration. Novel drug delivery technologies have

various advantages over traditional drug delivery systems.

Chemical property of ciprofloxacin

- Ciprofloxacin's chemical name is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. C17H18FN3O3 is its empirical formula, and its molecular weight is 331.4 g/mol. It is a crystalline substance that ranges from faintly yellowish to light yellow.
- Ciprofloxacin hydrochloride (USP) is the monohydrochloride monohydrate salt of ciprofloxacin. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8 g/mol. Its empirical formula is $C_{17}H_{18}FN_3O_3HCl•H_2O$.

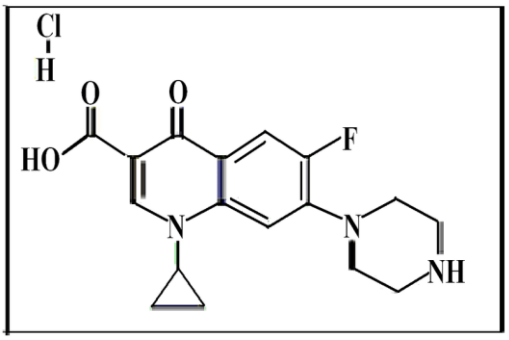

Fig 1: Chemical structure of Ciprofloxacin Hydrochloride

Mechanism of Action ciprofloxacin

Ciprofloxacin belongs to the fluoroquinolone drug class and is a bactericidal antibiotic. It prevents DNA replication by inhibiting the enzymes bacterial DNA topoisomerase and DNA gyrase. Ciprofloxacin is the most effective fluoroquinolone antibiotic against gram-negative bacilli (particularly Enterobacteriaceae such as Escherichia coli, Salmonella spp, Shigellaspp, and Neisseria gonorrhoeae).[2] Ciprofloxacin is also effective against certain gram-positive bacteria. Among the quinolones, ciprofloxacin is the most effective against Pseudomonas aeruginosa.[3] Progression of susceptibility to P. aeruginosa has been reported in Europe, North and South America, primarily in hospital or nursing home settings with identifiable risk factors. Ciprofloxacin is readily absorbed but typically does not achieve complete absorption Ciprofloxacin is one of the few oral antibiotics that can treat P. aeruginosa infections.[3]

Route of Administration of ciprofloxacin.

Ciprofloxacin is a drug that can be taken mostly orally or intravenously.

1. **Oral route:** Ciprofloxacin is taken twice a day for 7 to 14 days, or for at least two days after the infection's signs and symptoms have disappeared. For mild to moderate urinary tract infections, 250 mg twice daily is advised, and for severe or complicated infections, 500 mg twice daily is recommended. 500mg twice-daily dose is required for mild to moderate respiratory tract or skin and soft-tissue infections. For severe or difficult illnesses, a dosage of 750mg twice daily is suggested. To avoid gastrointestinal disturbance, Ciprofloxacin should be taken with food. In comparison to ciprofloxacin tablets, topical ciprofloxacin is a safe and effective antibiotic for the treatment of chronic otitis media.[5]
2. **Intravenous route:** For mild-to-moderate infections, an intravenous dose of 200 to 400 mg twice daily is recommended, and for severe, life-threatening infections, an intravenous dose of up to 400 mg every 8 hours is recommended.[4] For patients with severe renal impairment (creatinine clearance = 1.2 L/hour), a 50% reduction in daily dosage is recommended. Ciprofloxacin is given intravenously in a 60-minute slow infusion. It is critical to maintain adequate hydration and urine output

Contraindications of ciprofloxacin antibiotic

- Patients with documented hypersensitivity to the drug or formulation components are contraindicated for ciprofloxacin.
- The concurrent administration of tizanidine for muscle spasms is also a contraindication. The pharmacokinetics of tizanidine are altered by CYP1A2 inhibition (ciprofloxacin), leading to increased tizanidine levels and decreased psychomotor activity, blood pressure, and heart rate.[4][6]
- Avoid ciprofloxacin and its fluoroquinolone class in patients with myasthenia gravis because it may exacerbate muscle weaknesses.
- Ciprofloxacin is also considered to be contraindicated in children (except for the indications outlined above), in pregnancy, to nursing mothers, and in people with epilepsy or other seizure disorders.
- serum levels of the antiepileptic drugs phenytoin and carbamazepine (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

Interactions of ciprofloxacin antibiotic

- Ciprofloxacin interacts with certain foods and several other drugs leading to undesirable increases or decreases in the serum levels or distribution of one or both drugs.
- Ciprofloxacin should not be taken with antacids containing magnesium or aluminium, highly buffered drugs eg. (sevelamer, lanthanum carbonate, sucralfate, diagnosing). Magnesium or aluminium antacids turn ciprofloxacin into insoluble salts that are not readily absorbed by the intestinal tract, reducing peak serum concentrations by 90% or more, leading to therapeutic failure.
- Ciprofloxacin should not be taken alone with dairy products or calcium-fortified juices because it can reduce peak serum concentration and the area under the serum concentration-time curve by up to 40%. Ciprofloxacin, on the other hand, can be taken with dairy products or calcium-fortified juices as part of a meal.

EFFECT OF NOVEL DRUG DELIVERY APPROCH ON CIPROFLOXACIN

There are several advantages of novel drug delivery systems of ciprofloxacin over conventional drug delivery of ciprofloxacin.

- Optimum therapeutic- ciprofloxacin concentration in the blood or in tissue may be maintained over a prolonged period.
- Pre- determined release rates of extended period of time may be achieved.
- The duration of ciprofloxacin with a short half-life may be extended. Frequent dosing and medication waste may be substantially reduced.
- By targeting the site of action, side effects may be eliminated.
- Better patient compliance may be ensured.

A variety of novel carriers have been established and documented to be useful for controlled and targeted drug delivery. It is essential to critically evaluate the various terms used under the various broad categories of novel drug delivery systems.[7]

- **Sustained/controlled-drug delivery systems:** deliver drugs at a predetermined rate by releasing them at therapeutically effective levels in the circulation at a prolonged or constant (Zero-order) rate.
- **localised drug delivery systems:** Drug action is achieved by spatial or temporal control of drug release (typically rate-limiting) in the region of the target in localised drug delivery systems.
- **Rate-pre-programmed drug delivery systems:** manage the molecular diffusion of drug molecules and thereby offer drug action by regulating the release of drug molecules.
- **Targeted drug delivery systems:** Involves the use of carriers for passive or active targeting, or a single base or self-programmed method, which is usually anchored with appropriate sensory devices that detect the target's receptor.

NOVEL CARRIER FOR CONTROLLED & TARGETED DRUG DELIVERY

The majority of drugs are administered using conventional immediate-release dosage forms. They distribute freely throughout the body & accumulate the non-specific organs in an undesirable manner and thus produce adverse side effects. To reduce these slides and increase their therapeutic benefits, they must be delivered to their respective site of action, which necessitates the use of suitable carrier systems. Several new carriers have been developed for this purpose. Among these colloidal carriers, liposomes, Ethosomes, nanoparticles, and supra-molecular systems such as micelles, have received increased attention in the field of controlled and targeted drug delivery. Inorganic particles, liquid crystals, aquasomes, carbon nano tubes, dendrimers, and other novel carriers have recently been investigated for specialised applications. These carriers for the same purpose are discussed in detail in the following section.[7]

Colloidal carrier:

1. Liposomes: A liposome is a spherical vesicle having at least one lipid bilayer. Liposomes most often composed of phospholipids, especially phosphatidylcholine, but may also include other lipids, such as egg phosphatidylethanolamine, so long as they are compatible with lipid bilayer structure. The mechanism of delivering drugs is either by fusing with the cell membrane and releasing the drug or by endocytosis mechanism of the cells. Depending on the method of preparation, the vesicles can be multilamellar, small unilamellar, or large unilamellar. For targeting, the surfaces of liposomes are attached with ligands specific to the target site.[8]

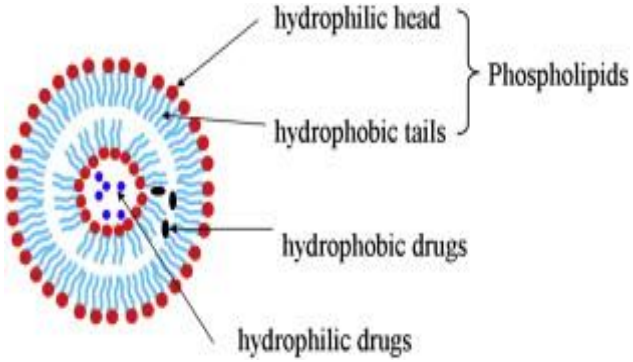

Fig 2: structure of Liposome.

Table 1: Types of liposomes used for different applications.[8]

Types	Uses
Conventional liposomes	Targeted delivery to macrophages and in vaccines
Cationic liposomes	Gene delivery
pH sensitive liposomes	Targeting tumours and in endocytosis
Temperature Sensitive liposomes	Site specific delivery of solid tumours
Immuno liposomes	Receptor mediated endocytosis

Table 2: Liposomes formulations of ciprofloxacin [9] [10]

Drug	Dosage form	Composition	Method	Use
Ciprofloxacin	Liposomal hydrogel	Phosphatidylcholine (pc) and cholesterol	The thin-film hydration method	Improving the topical bioavailability of ciprofloxacin hydrochloride to treat various skin disorders.
Ciprofloxacin	Ocular ciprofloxacin hydrochloride mucoadhesive chitosan-coated liposomes	phosphatidylcholine (pc), cholesterol (ch), stearylamine (sa) and dicetyl phosphate (dp)	The thin-film hydration method	Improve the ocular bioavailability of ciprofloxacin hydrochloride (cpx) through the preparation of ocular mucoadhesive chitosan (cs)-coated liposomes.

2. Ethosomes: Ethosomes are phospholipid-based lipid vesicles with a high concentration of alcohol (ethanol or isopropyl alcohol) and water. Ethanol (20 to 50%) acts as a penetration enhancer, allowing drugs to reach the deeper layers of the skin. The high concentration of ethanol is considered to be the reason for improved skin penetration. Ethanol increases the cell membrane fluidity and decrease the lipid density. Drugs including hormones, DNA, peptides can be incorporated in ethosomes.

Table 3: Ethosome formulations of ciprofloxacin [11]

Drug	Dosage form	Composition	Method	Use
Ciprofloxacin	Ethosomal Gel	Phosphatidylcholine (PC) from soybean lecithin, ethanol	Cold method	skin disorders.

3. Niosomes: Niosomes are vesicular structures with sizes ranging from 10-1000 nm that are formed by the incorporation of non-ionic surfactants and can be used to deliver amphiphilic and lipophilic drugs. Niosomes are non-toxic, biodegradable, more stable, and less expensive.[8] The main difference between liposomes and niosomes is that liposomes are made up of phospholipids, which contain two hydrophobic tails whereas niosomes are made up of non-ionic surfactants, which usually contain a single hydrophobic tail.

Table 4: Niosome formulations of ciprofloxacin [8]

Drug	Composition	Method
Ciprofloxacin	Tween 40 Span 40	Film hydration and pH and ammonium sulphate gradient35

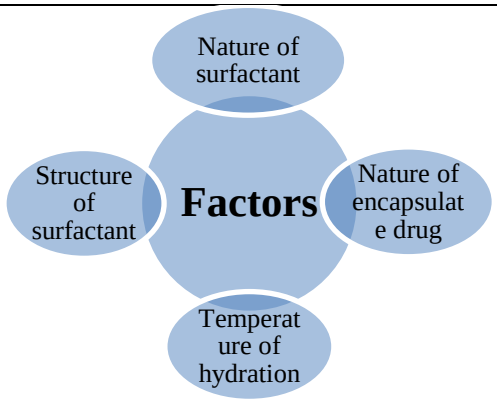

Fig.3: factors influencing niosomes physical stability.

4. Microparticles: Microcapsules are spherical particles with a core substance that range in size from 50 nm to 2 nm in diameter. Microspheres are spherical empty particles in the real sense. Microcapsules and microspheres, on the other hand, are commonly used interchangeably.

Table 5:Microparticles formulations of ciprofloxacin[12]

Drug	Dosage form	Composition	Method	Use
Ciprofloxacin	ciprofloxacin chitosan and pectin microspheres	pectin and chitosan	spray-drying method	osteomyelitis

5.Transferosomes: Transferosomes are ultra-deformable vesicles with a bilayered structure that are commonly used to deliver high molecular weight peptides, hormones, and various drugs. Due to their high flexibility, permeation becomes easy through the stratum corneum. Transferosomes squeeze through the stratum corneum's intracellular lipid and penetrate into the skin layers, bypassing their barrier function. Osmotic gradients in the skin layers also enable the movement of vesicles from the dry stratum corneum (top layer) to the hydrated deeper layers of the skin.

Table 6: Transferosomes formulations of ciprofloxacin[13]

Drug	Dosage form	Composition	Method	Use
Ciprofloxacin	Nano-transfersomal ciprofloxacin loaded vesicles	Phospholipid and sodium cholate	thin film hydration	1. Treatment of otitis media in adults. 2. Topical treatment of otorrhea in children

6.Microemulsion: Microemulsions are thermodynamically stable fluids, as compared to kinetically stable emulsions, which separate into oil and water over time. Microemulsions have particle sizes ranging from 10 to 300 nanometers. Microemulsions appear as clear or translucent solutions due to their small particle size.

Table 7: Microemulsion formulations Of Ciprofloxacin

Drug	Dosage form	Composition	Use
Ciprofloxacin	Ciprofloxacin Microemulsion	Isopropyl Myristate, Polysorbate 80, Ethyl Alcohol and Water	Reduction Of S. Aureus Nasal

			Colonization and Skin Infection.

Table 8: list of ciprofloxacin formulations based on novel drug delivery systems [14-25]

Drug	Dosage form	Composition	Use
Ciprofloxacin	Ciprofloxacin hydrogels based on an ionic complex	Dendronized polymer	Treatment of topical and mucosal opportunistic infections in human or veterinary applications.
Ciprofloxacin	Povidone foils and nanofiber mats	Polyvinylpyrrolidone (pvp) and acetic acid as a solubilizer.	Chronic wounds infections
Ciprofloxacin	Ciprofloxacin monoolein water gels	Glycerol monooleate, Deionized water	treatment of chronic osteomyelitis

CONCLUSION

This article outlines about liposomes, niosomes, ethosomes and transferosomes of ciprofloxacin drugs and its merits over the conventional formulations. Novel Drug Delivery System (NDDS) NDDS is a combination of advanced technique and new dosage forms that are far superior to conventional dosage forms. Advantages of Novel Drug Delivery System include optimum dose at the right time and right location, efficient use of expensive drugs, excipients, and cost reduction in production, benefit to patients, better therapy, improved comfort, and standard of living. The following are the fundamental modes of novel drug delivery systems: Targeted Drug Delivery System, Controlled Drug Delivery System, etc. Novel drug delivery and drug targeting are new techniques used in pharmaceutical science. Targeted drug delivery, vaccine delivery, and gene therapy are examples of commercial development of novel carries (liposomes).

REFERENCES

1) Sharma, Jain A, Jain S, Pahwa R, Ciprofloxacin: Review on Developments In Synthetic, Analytical, And Medicinal Aspects. Med Chem. 2010 Aug;25(4):577-89.
2) Campoli-Richards Dm, Monk Jp, Price A, Benfield P, Todd Pa, Ciprofloxacin. A Review of Its Antibacterial Activity, Pharmacokinetic Properties and Therapeutic Uses Drugs, 1988 Apr;35(4):373-447.
3) Lebel M., Ciprofloxacin: Chemistry, Mechanism of Action, Resistance, Antimicrobial Spectrum, Pharmacokinetics, Clinical Trials, And Adverse Reactions. Pharmacotherapy. 1988;8(1):3-33.
4) Davis R, Markham A, Ciprofloxacin an Updated Review Of Its Pharmacology, Therapeutic Efficacy And Tolerability, Drugs. 1996 Jun;51(6):1019-74.
5) Samarei R, Comparison of Local and Systemic Ciprofloxacin Ototoxicity In The Treatment Of Chronic Media Otitis, Glob J Health Sci. 2014 Sep 18;6:144-9.
6) Abd-Elsayed A, A Severe Interaction BetweenTizanidine and Ciprofloxacin, J Clin Anesth. 2015 Dec;27(8):698.
7) MohdGayoor Khan, The Novel Drug Delivery System, World Journal of Pharmacy and Pharmaceutical Sciencesvolume 6, Issue 7, 477-48.
8) M. UdayaSakthi, D. Ramya Devi, B. N. VedhaHari, Vesicular Mode of Drug Delivery: A Promising Approach for Anti-Infective Therapy, International Journal of Chemical Sciences · January 2014 12(3), 2014, 797-814.
9) Paul Et Al., Formulation and Evaluation of Ciprofloxacin Hydrochloride Encapsulated Liposomal Hydrogel for Dermal Administration, Ijpsr, 2021; Vol. 12(6): 3249-3256.
10) GhadaAbdelbar,Ocular Ciprofloxacin Hydrochloride Mucoadhesive Chitosan-Coated Liposomes,Pharmaceutical Development and Technology Volume 16, 2011.
11) Sahishta Khan, BkDubey, Gk Pandey, Amit Jain, Suresh Dhakar, Prabhat Kumar Jain, Formulation and Evaluation of Ethosomal Gel Of Ciprofloxacin For Bacterial Infections, National Journal Of Advanced Research, Volume 5; Issue 2; April 2019; Page No. 21-25.
12) Z. Orhan, E. Cevher, L. Mülazimoglu, D. Gürcan, M. AlperA. Araman, Y. Özsoy, Preparation Of Ciprofloxacin Hydrochloride-Loaded Chitosan And Pectin Microspheres The Journal Of Bone And Joint Surgery. British Volume 88-B, No. 2
13) Abdulaziz Mohsen Al-Mahallawi 1, Omneya Mohammed Khowessah 2, Raguia Ali Shoukri, Nano-Transfersomal Ciprofloxacin Loaded Vesicles For Non-Invasive Trans-Tympanic Ototopical Delivery: In-Vitro Optimization, Ex-Vivo Permeation Studies, And In-Vivo Assessment , Int J Pharm 2014 Sep 10;472(1-2):304-14.
14) Mónica C. GarcíaA , Julio C. Cuggino C , Clarisa I. Rosset A , Paulina L. Páez A , Miriam C. Strumia B , Ruben H. Manzo A , Fabiana L. Alovero A , Cecilia I. Alvarez Igarzabal B , Alvaro F. Jimenez-Kairuz , A Novel Gel Based On An Ionic Complex From A Dendronized Polymer And Ciprofloxacin: Evaluation Of Its Use For Controlled Topical Drug Release, Materials Science And Engineering C 69 (2016) 236–246.
15) Veronica Volpe, Ciprofloxacin Loaded O/W Microemulsion Against Staphylococcus Aureus.

Analytical And Biological Studies For Topical And Intranasal Administration, Journal of Drug Delivery Science and TechnologyVolume 57, June 2020.

16) Abdul.R.Siddiqui, Jack M. Bernstein, Chronic Wound Infection: Facts And Controversies. Clinics In Dermatology 2010 (28), 519–526.
17) FiorenzaRancan, Marco Contardi, Evaluation Of Drug Delivery And Efficacy Of Ciprofloxacin-Loaded Povidone Foils And Nanofiber Mats In A Wound-Infection Model Based On Ex Vivo Human Skin, Mdpi Pharmaceutics 2019 (11), 527.
18) Vijayakumar. K.Parthiban, Senthil kumar, Tamiz Mani, Ethosomes-A New Trend In Vesicular Approaches For Topical Drug Delivery, Asian Journal Of Research In Pharmaceutical Sciences And Biotechnology, 2014;2(1),23-30.
19) Londhe, Zaltoprofen Loaded Solid Lipid Nanoparticles For Topical Delivery Formulation Design. In Vitro And Ex Vivo Evaluation. Moj Bioequivalence & Bioavailability, 2017,4(2),24-31.
20) Gambaro, Perazella, Adverse Renal Effects of Anti-Inflammatory Agents: Evaluation Of Selective And Nonselective Cyclooxygenase Inhibitors, J Intern Med,2003,253(6),643–52.
21) Sean.C.Sweetman, Martindale The Complete Drug Reference", 34th Ed,London; Pharmaceutical Press, 2000,188-9.
22) Armstrong.R.A,The Microbiology Of The Eye, OphthalPhysiol Opt, 2000 (20),429-441.
23) Egger.S.F, Ruckhofer, Alzner. In Vitro Susceptibilities To Topical Antibiotics Of Bacteria Isolated From The Surface Of Clinically Symptomatic Eyes. Ophthal Res, 2001(33),117-120.
24) Hwang.D.G., Fluoroquinolone Resistance In Ophthalmology And The Potential Role For Newer Ophthalmic Fluoroquinolones, SurvOphthalmol, 2004(49),S79-S83.
25) Rancan.F. Drug Delivery to Skin By Nanotechnology-Based Drug Delivery Systems. J Pharm Drug DelivRes.2018(07),1-6.
26) Parashar.T, Sachan.R, Singh.V, Singh.G. Ethosomes: A Recent Vesicle of Transdermal Drug Delivery System. Int J Res Dev Pharma Life Sci. 2013,2(2), 285- 293.